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OCULAR SYMPTOMS AND COMPLICATIONS OBSERVED IN DENGUE*

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The epidemic of dengue which occurred in Florida and other Southern states during 1922 and 1923 afforded me an opportunity of observing many patients complaining of ocular symptoms during and subsequent to the infection, and of recognizing a number of interesting ocular complications. In 1923 I reported these observations to the Florida Medical Association. In 1926, in a paper read before the Eye, Ear, Nose and Throat Section of the Southern Medical Association, I reported in detail six cases of vesicular and dendritic keratitis complicating dengue. At that time no claim for priority was made, but a review of the literature

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on the subject failed to reveal the reports of similar cases. However, during the more recent epidemics of dengue which occurred in Greece and in Egypt in 1928 and 1929, similar cases of keratitis were recorded. In addition to the six cases of keratitis reported previously, I am adding reports of two cases of ocular muscle involvement, namely, one of ptosis and one of paresis of accommodation.

The uniqueness of the dengue infection, together with the fact that its occurrence is limited to the tropics and subtropics, justifies a brief description of its characteristics.

Dengue, also known as "break-bone fever" and "dandy fever," is an acute infectious disease caused by an ultramicroscopic filtrable virus. It occurs in epidemic and endemic forms in tropical and subtropical countries of both hemispheres. It is characterized by two more or less distinct febrile paroxysms, very severe pain in the muscles and joints, and an initial erythematous and a terminal protean rash.

The disease was first described in 1779 in Cairo and Java by Bylon. In 1780, when an epidemic occurred in Philadelphia, Benjamin Rush gave the first description of the disease in the United States. Since that time there have been nine epidemics in the United States, including the most recent ones in the Southern states in 1922 and 1923. In Greece the last epidemic of importance occurred in 1928. In the United States none of the recent epidemics extended north of the Mason and Dixon line.

The disease is transmitted by the mosquito. Experiments have shown that aedes aegypti and aedes albopictus are carriers. Ashburn and Craig, working in the Philippines, transmitted the disease by injecting whole or filtered blood. Cleland, Bradley, and McDonald produced dengue in volunteers by the injection of washed corpuscles as well as of serum and plasma, thus demonstrating that the virus is present in all the blood elements.

Several workers have reported finding in the blood organisms which they believed to be the cause of dengue. McLaughlin (1886) described a micrococcus he found in the blood of patients with dengue. Graham (1903) reported finding a hematozoön which he believed to be responsible for the disease. Holt (1922) described a polymorphous organism which he had seen in the blood. All these observations, however, lack confirmation.

The incubation period of dengue is from three to fourteen days, during which time the patient is apparently in normal health. The onset is usually sudden, with severe headache, chilly sensations, and pains in the muscles and joints. The temperature rises rapidly, and after a few hours reaches a height of from 102° to 106° F. Within one or two hours the initial rash appears. This may consist of a blotchy congestion of the face or a scarlatiniform erythema of the face and extremities. The eruption is usually a transient one. There is an intense headache of the supra-orbital and retrobulbar type. The conjunctivae are congested. Ocular movements are attended with discomfort. The pulse rate is rapid at the onset, but soon becomes slow, frequently dropping by the fourth or fifth day of the disease to 50 or 60. There are intense pains at the muscular insertions of the joints. Backache is severe, and general myalgia is characteristic.

Insomnia and severe mental and physical depression occur. Anorexia is common, as is also constipation. At about the third or fourth day the temperature usually returns to normal. After an interval varying from twelve hours to three days it rises again. During the remission the patient feels better and may attempt to return to work, only to be stricken with another febrile paroxysm similar to the first and attended with general discomfort, but in a lesser degree of intensity. In most instances the second rise of temperature is accompanied by a rash that is protean in character. It may be macular, like that of measles, or it

may be diffuse, scarlatiniform, or papular. The eruption, while it may vary, is almost always present. After the appearance of the terminal rash the temperature usually drops. In some instances diarrhea and epistaxis accompany the crisis-like drop of the temperature. During convalescence a furfuraceous desquamation occurs at the site of the terminal rash. The average duration of the attack is seven or eight days.

Leukopenia is a characteristic finding in dengue, Stitt finding the average white cell count to be 3,200. There is usually no change in the number or character of the red cells.

The prognosis is excellent, there being few complications that accompany dengue. The mortality is practically nil, and for this reason there has been no description of the anatomic pathology. As a rule, one attack renders a person immune. Dengue must be differentiated from yellow fever, measles, scarlet fever, influenza, pappataci fever, Brill's disease, Rocky Mountain fever, and malaria.

The records of the Florida State Board of Health show that during the months of July, August, September, and October, 1922, 25,192 cases of dengue were reported, and that in 1923 2,000 cases were recorded. Realizing the fact that the number of cases that occurred far exceeded the number reported, the State Board of Health sent a questionnaire to each physician in the state. The resulting estimate of the total number of cases was 82,681. The Jacksonville Health Department estimated that during the 1922 epidemic there were no fewer than 20,000 cases in Jacksonville. At that time the population of the city was about 100,000, so that at least 20 per cent. of the population were affected. Since the ocular symptoms are among the first and most annoying of those occurring during and subsequent to an attack of dengue, it is not surprising that the ophthalmologist should be interested in the disease. My case records for the year 1922–1923, and since, indicate that about 1,000

patients, seen while suffering from the disease or soon thereafter, complained of eye symptoms. In the literature I have been unable to find a complete bibliography concerning the ocular symptoms and complications of dengue, and for this reason I am appending a bibliography to this paper and quoting freely from the references.

In nearly all general descriptions of the disease mere mention is made of ocular symptoms occurring during the acute stage. Manson's "Tropical Diseases" disposes of the subject with the following statements: "The head and eyeballs ache excessively." "The face, particularly the lower part of the forehead, round the eyes and over the malar bones, may become suffused with a deep purple." "The eyes are usually much injected."

Elliot, in his textbook on "Tropical Ophthalmology," devotes only a few paragraphs to the eye manifestations of dengue, mentioning that such complications as keratitis, iridochoroiditis, amaurosis, and muscular paralyses have been ascribed to the disease.

Santos-Fernandez, writing on "Ocular Manifestations in Dengue" in 1900, states that he has not heard of any special study of the ocular symptoms of the disease. Such manifestations, he asserts, had been reported, but only incidentally. In common with others this author mentions pain in the eyes, and occasionally photophobia, as characteristic symptoms of the early stage of the disease; at this stage the eyes appear to be "brilliant and congested." During convalescence, Santos-Fernandez notes some diminution of vision, which he attributes to paresis of the muscle of accommodation. He also notes a "special alteration of the vision" in which all objects appear to be red or yellow, a condition which is due, he believes, to "hyperesthesia of the retina." In his six cases of this type the patients "saw all objects as if they were illuminated by the glare of a great conflagration."

Barkan reported a case of paralysis of the external rectus and one of paresis of accommodation following dengue. Commenting further on the ocular phases of dengue, he stated: "In dengue we are acquainted with one constant ocular symptom, the intense aching of the eyes, whether a true myalgia or a slight degree of serous tenonitis, or periostitis, is uncertain. It is rather surprising that ocular complications, such as the two cases of muscular paralysis I report, are not more common. There are many similar points in dengue and influenza. With the existing similarities, it is curious that dengue has not been known to be complicated by the ocular diseases commonly reported in association with influenza. One need only think of acute hordeolum, keratitis neuroparalytica, herpes corneae, keratitis punctata superficialis, neuritis optica, muscular paralysis, iritis, etc."

Gibson reported that during the epidemic of dengue in Brisbane, Australia, in 1905, he saw three cases of keratitis complicating prolonged or relapsing attacks of the disease, and five cases of keratitis occurring after the attack of dengue had subsided—usually during the first weeks of convalescence. This author describes the post-dengue keratitis as follows: "In its most typical form, a triangular area of the cornea is affected, with its base at the periphery and its apex at or beyond the center of the cornea. At its onset there is acute pain, with photophobia and lacrimation. The corneal epithelium is possibly raised as a bleb at the extreme outset, but this I have not seen; it, or a superficial layer of it, seems then to slough and to leave a very shallow ulcer in whose floor appear a number of pinhead opacities apparently situated in the more superficial layers of the interstitial substance of the cornea. In the worst cases the triangular layer involved a fourth of the cornea; in the least severe, there was a very narrow triangle."

After the first few hours of hyperesthesia the affected area

of the cornea was anesthetic, and this anesthesia persisted for some time—in one case for more than two months. In the cases in which keratitis developed during the attack the superficial ulceration was more extensive, and the iris was so irritable as to require the continued use of a mydriatic. The post-dengue cases were "evidently due to peripheral neuritis of that portion of the corneal nerve plexus corresponding to the affected area with resulting keratitis neuroparalytica." In those cases of keratitis occurring during the attack of dengue, ulceration, probably due to the microorganism of dengue itself, was added to the neuroparalytic condition. This accords with the observation that peripheral neuritis in other parts of the body is not infrequently observed during convalescence from dengue. In this epidemic a large percentage of the population of Brisbane was attacked by dengue, yet Gibson observed only eight cases of keratitis complicating the disease and heard of no others. He concludes that keratitis is an extremely rare complication.

Van Steeden in 1907 reported one case of dengue in which papillitis and paresis of accommodation occurred. Both conditions cleared up in about two months.

Riad (1929) stated that during the recent epidemic of dengue in Egypt he saw nine patients with eye complications. Of these, six had keratitis, one phlyctenular conjunctivitis, one iritis, and one paresis of accommodation. In these cases the corneal lesions began on the third or fourth day after the onset of fever; in some instances the lesions appeared as small gray infiltrations scattered irregularly in the cornea, or occurred in the upper part of the cornea in a "horseshoe" arrangement, surrounded by superficial blood vessels; or as small vesicles that had ruptured, leaving small superficial ulcers; or as a single large bleb that broke down to form a larger superficial ulcer. The corneal lesions were always accompanied by photophobia, lacrimation, and pain, with

ciliary injection. Four of the six cases with corneal lesions had a herpetic rash on the eyelids, the ala of the nose, and part of the face on the same side as the affected eye, which developed one day before the corneal lesions. The corneal lesions healed, in some cases leaving a nebula or leukoma.

Bistis (1929) published an article concerning the epidemic of dengue in Athens, in which he said that keratitis punctata, keratitis dendritica, iritis, glaucoma, and retrobulbar neuritis had been mentioned as complications. In the majority of the cases a conjunctival catarrh, with reddening of the conjunctiva of the eyelids, developed on the third or fourth day of the disease. The inflammation was accompanied by a slight secretion which collected in the internal canthus. The patients complained of severe burning of the eyes. Bistis did not observe other catarrhal complications, such as ulcers of the cornea.

In one of the cases described by Bistis there was paralysis of the external rectus muscle, with resulting right-sided homonymous diplopia, which developed shortly after the cessation of the fever. This persisted for a month and disappeared without treatment. In several cases he noted a paresis of accommodation that made reading difficult. The condition disappeared after six weeks. Bistis regards the paralyses and pareses which complicate dengue as neuritic manifestations, just as he does the general polyneuritic complications which accompany this infectious disease.

In another of Bistis' cases there was a retrobulbar neuritis. On the second day after the cessation of the fever—hence on the ninth day after onset—the patient was unable to read. Examination of the field of vision showed a central absolute scotoma. Examination of the eyegrounds revealed nothing abnormal. The scotoma was present for a month.

During the same epidemic Anargyros reported five cases with ocular complications. In each of these cases there was an exanthem. The first case was a dacryoadenitis of the

left eye, with swelling of the preauricular and parotid glands. The second case was an iritis of the left eye which appeared on the sixth day. In the third case there were retinal hemorrhages in a patient who had had albuminuria during the course of the dengue. Fifty days after the appearance of the visual disturbance the hemorrhages were almost completely absorbed. In the fourth case, glaucoma of the left eye appeared on the fourth and last day of the fever, simultaneously with the appearance of the exanthem, and two days later there was a less severe attack of glaucoma in the right eye. Iridectomy was done, first in the left, then in the right, eye. The fifth patient, aged fifty-four years, had two years previously lost the sight of the right eye from glaucoma. The eye had remained painless until convalescence from dengue took place, when the conjunctiva became injected and there was intense pain. The eye was enucleated and the vitreous body was found to be full of blood clots.

In some patients pain in the eyes, so frequent in dengue, was intense, especially during movements of the eye. Anargyros also observed hordeola and, still more frequently, copiopia or accommodative asthenopia lasting from several days to several weeks. In two patients with scintillating scotoma the attacks became more frequent and continued for a longer period of time after dengue.

Charamis observed two cases of dengue with orbital pain "behind the globe," intense photophobia, and slight myosis lasting from eight to ten days. In another case there were periorbital pains, with trigeminal pains on the sides of the head and face. In these cases spots appeared before the eyes. In one patient this symptom, attenuated, persisted after recovery. There were two cases with classic optic neuritis; in one instance this continued for a month after recovery from dengue and in the other instance it disappeared immediately on recovery. There were several cases of ulcerative keratitis. As in Lyritas' observations, there were small

peripheral ulcerations, most of which resulted in maculas. In one patient ulceration led to perforation of the cornea with prolapse of the iris and staphyloma. The conjunctivitis was generally relieved by the usual treatment. Several more or less severe cases of temporary amblyopia were observed.

Gabrielides found the following ocular symptoms appearing during the acute course of dengue: conjunctivitis, muscular pains, and blepharitis. The symptoms that occur during and after convalescence are: copiopia and asthenopia, due to weakness of the muscle of accommodation; diplopia; "entoptic phenomena"—spots before the eyes, photophobia, scintillating scotoma; keratitis, and iritis.

During the last epidemic in Athens Gabrielides saw a number of cases of conjunctivitis, accompanied in some instances by redness of the face, which appeared at the beginning, during the course of the fever, or coincident with the final exanthem, and which persisted sometimes even after the final eruption. The secretion was not abundant. The organisms found on the third, fourth, and sixth days were the bacilli xerosis, which occurred in abundance, alone, or accompanied by a gram-negative coccus.

In one case observed during the epidemic in Athens, that of a man eighty years of age, there appeared, on the third day of convalescence, acute parotitis with fever. Incision of the parotid yielded a thick pus. There was severe edema of the left eyelids, accompanied by conjunctivitis. At the same time, in the lower part of the cornea in the immediate vicinity of the limbus, superficial keratitis was observed. In the right eye there was slight conjunctivitis without corneal involvement. Smears and cultures showed bacilli xerosis in great abundance and a few diplobacilli of Morax. In this case there was a pre-existing diplobacillary conjunctivitis which, after the dengue and on the occasion of the parotitis, gained virulence and finally attacked the cornea. Gabrielides believes that the ulcerative keratitis attributed to

dengue is due to other organisms, and has no direct relationship to the micro-organisms of dengue. Being a disease with an exanthem, dengue naturally would be complicated by superficial punctate keratitis strictly epithelial in localization.

Among the patients examined during the exanthematous stage of dengue, Gabrielides did not find one case of superficial punctate keratitis, but he did see a case (previously reported) in which punctate keratitis developed in a syphilitic patient after an attack of dengue. If the history had not been known, the keratitis would have been attributed to dengue, but in 1914 this patient had been treated for episcleritis due to syphilis. Gabrielides is of the opinion that in this case the keratitis was due to an old syphilitic infection, rather than to the dengue, especially as it was unilateral and persisted for some time, being evident forty-five days after onset, whereas the punctate keratitis of exanthematous diseases is usually bilateral and of short duration. In this case it is impossible to determine whether the dengue infection played any rôle in the development of the keratitis. In such cases of punctate keratitis associated with dengue Gabrielides believes that the keratitis should not be attributed entirely to dengue without careful study, keeping in mind especially the possibility of a latent syphilis or tuberculosis which may be the underlying cause of the keratitis. This observer admits, however, that dengue may be the cause of either keratitis or iritis. In one of his cases dengue was undoubtedly the cause of an iritis that developed twenty days after the acute attack. The Wassermann, Sachs-Georgi, and Mueller tests were negative. The iritis was successfully treated with atropin alone. The iritis caused comparatively mild symptoms, some pain, and discrete synechias. In one patient, a woman, dengue had no effect on an existing keratitis and iritis.

In another patient, a young girl, in the last days of the fever and the first days of convalescence, Gabrielides noted

a fleeting diplopia. This was due to paresis of the left external rectus. In a woman, aged seventy years, there was a diplopia during the last days of fever. During convalescence the diplopia became less troublesome. On the eighth day it reappeared, and on the tenth day it finally disappeared. There was an insufficiency of the left external rectus. Aside from these cases of muscular asthenia, Gabrielides observed no true pareses or paralyses of the ocular muscles.

In two young girls seen by Gabrielides there was copiopia due to an accommodative asthenia. They also complained of headaches and spots before the eyes. In one woman, twenty-four years of age, there was scintillating photopsia, which began two days after the fever subsided. It was limited to the external portion of the visual field of the right eye, and lasted thirteen days. It gave rise to headaches, nausea, and vertigo. Examination of the eye revealed nothing abnormal. In the past the patient had had similar photopsia, accompanied by vomiting. The onset of menstruation marked the disappearance of the trouble.

Gabrielides observed two cases of glaucoma in women aged sixty and fifty-four years respectively. In the first case symptoms appeared on the third day; in the second case the symptoms, with the complete loss of vision, appeared on the fourth day. Notwithstanding intensive treatment, the glaucomatous phenomena, and especially the pupillary dilatation, persisted. In the first case there was a deposit of black pigment on the anterior capsule of the lens, without inflammatory phenomena. In one man, aged sixty years, who had had a previous attack of glaucoma, there was an absolute glaucoma. There was one case of recurring retinal hemorrhage in a woman, aged fifty years, who had had retinal hemorrhages for seven years. After eight months of quiescence hemorrhages reappeared immediately after an attack of dengue. This attack, of course, could not be attributed entirely to the disease. Optic neuritis occurred in

one man, aged fifty-two years, during convalescence from dengue, ten days after the exanthematous eruption. In six days all vision in this eye was lost. Under treatment with leeches applied to the left temple he regained some vision. After two and a half months the vision of the eye had improved still more and was as good as it had been before the attack of dengue. The vision of the left eye had never been equal to that of the right eye.

In his discussion of my paper read before the Southern Medical Association in 1926, Gill reported that, during the summer of 1923, 1241 patients with dengue were admitted to the Station Hospital at Fort Sam Houston, San Antonio, Texas. This group of patients was subjected to a special study by the Eye Department of the Station Hospital. In every patient retrobulbar pain was present and was considered to be due to a myositis of the extra-ocular muscles, similar in type to that associated so frequently with influenzal infections. In every patient conjunctival congestion or suffusion was present in some degree. There were usually slight photophobia and excessive lacrimation associated with the congestion. Bacteriologic investigation of smears and cultures from the conjunctivae of 11 patients in whom there was a catarrhal discharge was negative. Many patients showed a congestion of the retinal vessels, which was localized principally in the veins. The conjunctival congestion, as well as the retinal congestion, may be due, Gill believes, to the effect upon the vasomotor mechanism of a toxin liberated by the organism of dengue.

Bargy (1929) observed that except for the conjunctivitis and pains in the ocular muscles in the early stage of the disease, dengue rarely affects the eye. In the course of seventeen years he saw "several hundred" cases of dengue, but in only four cases were there ocular complications that could be attributed to dengue, including two cases of corneal herpes, one case of paresis of the third cranial nerve, and one case

of retrobulbar neuritis. "Corneal herpes," he says, "is a frequent complication of all fevers; hence it is not remarkable that it should be observed in dengue." Bargy's four case reports follow:

1. A boy, aged twelve years, on the fourteenth day of a moderately severe attack of dengue, developed photophobia, excessive lacrimation, and severe pain in the right eye. Examination showed several small vesicles on the cornea. Fifteen days later there were two small ulcers on the cornea—one central, with irregular borders from which ramifications extended (dendritic appearance). The lesions were superficial, with no trace of vascularization. They healed after three weeks, with slight scarring.

2. The patient was a man, aged forty years. On the twentieth day of the attack of dengue the first eye symptoms developed. He had had two previous attacks, in 1915 and in 1917. In both, pain and photophobia in the right eye occurred during convalescence. During these attacks the condition was diagnosed as ulceration of the cornea. In the present attack, occurring in October, 1920, at the time of an epidemic of dengue, the same symptoms developed in the right eye on the twentieth day after onset. There was no improvement within ten days, and the patient was examined by Bargy. A scar of a previous dendritic ulceration, which the patient said resulted from the attack in 1915, and acute ulceration, definitely dendritic in form, were found. There was hyperesthesia of the cornea, but no vascularization. There was a pinpoint pupil, but it could be dilated with atropin. In fifteen days there was a definite improvement, after which a slight exacerbation of the corneal lesion occurred, with complete recovery in three weeks.

3. In this case of paresis of the third cranial nerve the patient was a boy of sixteen years. On the twenty-fifth day after the onset of a severe attack of dengue he found reading difficult. Examination showed a marked diminution of accommodation affecting the left eye only; there was also a slight mydriasis of the left pupil, and a delay in the movement of lifting the upper eyelid on the left side. The patient stated that four days before he had noticed also a temporary diplopia. After about three weeks of treatment recovery was complete.

4. In the case of retrobulbar neuritis the eye symptoms were

similar to those observed in two cases of measles seen many years before. The patient had had a severe attack of dengue, with two relapses. On the twenty-sixth day after onset he noted a blurring of the vision of the left eye. Examination showed a central scotoma, limitation of the field of vision, and abnormalities of color vision (red seen as brown, but blue and green normal). Pressure on the eyeball produced slight pain. The ophthalmoscopic examination showed a slight venous congestion of the retinal vessels and some blurring of the optic discs in their temporal segment. There was no evidence of syphilis or of sinusitis. Improvement was noted within ten days; within forty days the scotoma disappeared, and vision gradually became entirely normal.

In the discussion of Bargy's paper Trantas stated that during the epidemic of dengue in Athens he had observed several cases of keratitis complicating dengue, including dendritic keratitis, keratitis disciformis, annular marginal keratitis, and more frequently superficial punctate keratitis without subjective symptoms. He also saw several instances in which glaucoma occurred in association with dengue. Instances of iritis were extremely rare. He had observed none of metastatic ophthalmia, but had seen several of optic neuritis—one with a central scotoma.

Apostolopoulos (1930) noted the following eye complications as observed in the dengue epidemic at Athens: hemeralopia, diplopia, amaurosis (temporary), and failure or weakness of accommodation. Bensis (1931), in discussing the recent epidemic of dengue in Athens, stated that, in addition to the conjunctivitis observed in dengue, superficial keratitis was found. Lesions of the fundus were rare. Ghiannoulatos (1931) reported a case of dengue observed during the Athens epidemic of 1928 in which a typical attack of the disease was followed by severe polyneuritis with paralysis of both upper and lower extremities (pseudotabes), the first symptoms being noted on the tenth day. The eye symptoms included an intermittent diplopia without evident paralysis of the muscles, a slight amblyopia, and a mild optic

neuritis. The eyelids did not close completely. The paralysis began to improve within a month, but three months elapsed before the patient could walk normally, and nearly a year elapsed before the eye symptoms entirely disappeared.

In my own experience the ocular symptoms in the active stage of dengue were in most instances prominent. Intense retrobulbar aching was the most constant finding, occurring in 80 per cent. of the patients observed. Associated with this there was frequently a feeling of tension within the globes, the patients describing it as "feeling as if my eyeballs will burst." Supra-orbital neuralgia occurred in 25 per cent. of the patients. Ocular pains were intensified by movements of the eyeballs.

Lacrimation, photophobia, and a feeling as of sand under the lids were complained of by 75 per cent. of my patients. These symptoms were undoubtedly due to the suffusion of the conjunctiva, which is almost a constant accompaniment of the disease and affects uniformly the ocular and palpebral conjunctivae. In many patients a slight purulent discharge was present, in a few instances being profuse enough to simulate acute conjunctivitis. However, organisms which would account for the conjunctival congestion and discharge were not found in microscopic examination of the discharge. In a series of 100 patients smears and cultures taken from the conjunctival sac were negative except for the presence of pus cells and organisms normally found in the conjunctival sac.

In a series of 100 patients fields and blind-spots were studied, with normal recordings. These patients were examined within one week after the subsidence of an acute attack of dengue. Ophthalmoscopic examination of 100 patients in the same series showed no changes which could be attributed to the disease. The ocular tension was consistently normal, as were the pupillary reactions.

In 1923 I reported six cases of dendritic and vesicular

keratitis complicating dengue. In 1927 these case reports were published in detail. I have been unable to find in the literature similar types of keratitis occurring before the Greek epidemic of 1928. The six cases of keratitis, of which five are reported here, occurred during the first week of convalescence. In each instance it was established clinically that the patient had suffered from dengue. Four of the cases were of the typical dendritic variety, the corneal lesions assuming a characteristic arborescent conformation. The other two cases were of the vesicular type, the lesions never coalescing. None of the cases was complicated by iritis or hypopyon. In three of the patients, partial anesthesia of the cornea was observed, whereas the other three had unimpaired corneal sensation. In all instances the corneal lesions were unilateral.

The patients laid great stress on the ocular discomfort they had suffered during the acute stage of the disease. Direct smears and cultures failed to reveal any organisms other than a few pus cells. Three of the patients recovered within two weeks with no impairment of vision. One case persisted over a period of three months, vesicles forming in successive crops and ultimately reducing the vision from 6/6 to 6/12 because of a central opacity which resulted. Two cases, which were of three weeks' duration, terminated with a very slight reduction in vision as a result of nebular opacities. Three cases of herpes of the eyelids were seen, one of which occurred in one of the cases of dendritic keratitis mentioned above. Two of the patients showed herpes of the lips; in one, in addition to the lesion of the lips, there was involvement of the ala of the nose. In each case the herpes was unilateral.

I submit the following case histories for consideration:

CASE 1.—A white female, aged sixty-five years, consulted me in October, 1922, complaining of photophobia, lacrimation, retrobulbar neuralgia, and a feeling as of sand under the eyelids. The

patient stated that eleven days previously she had become suddenly ill, with a slight chill and nausea, which was followed in a few hours by elevation of temperature to 102° F. The family physician was called, and made a diagnosis of dengue. The elevation of temperature continued for three days, during which time headache and retrobulbar neuralgia were intense, as was also the aching of the bones. The eyes were congested and there was marked photophobia. During this period the patient was confined to bed. After three days the fever subsided, but recurred on the fifth day, with a repetition of the acute symptoms, and in addition a rash of the arms, chest, and thighs, which itched intensely. The second elevation of temperature lasted about twenty-four hours, after which she felt listless and the bone pains continued. On the tenth day there was pain in the left eye, and a feeling as of sand under the eyelids, with photophobia, lacrimation, and supraorbital neuralgia of an almost unbearable severity.

The family history was negative. In 1900 and 1904 she had had malaria. For eighteen years a lump had been present on the left side of the neck, which her physician told her was a cystic goiter. A general physical examination was negative, except for a cystic goiter about the size of a hen's egg on the left side. Wassermann, urinalysis, and examination for malarial plasmodium were negative.

The patient showed intense lacrimation and photophobia. The right eye was normal in all respects, with vision of 6/6 with correcting lenses. The left eye showed an injection of the ocular and palpebral conjunctivae, which was accentuated at the limbus. Above the center of the cornea were five vesicles, each about the size of a pinhead. Staining with fluorescein showed that three of the vesicles had ruptured. Surrounding each vesicle was a narrow line of infiltration. There was partial anesthesia of the cornea. The iris was normal in appearance; the pupil reacted normally. Vision was 6/9 with correcting lenses. The tension was 20 mm. Hg (Schiötz).

Fomentations, 1 per cent. atropin, and 2 per cent. holocain, every three hours, were ordered. Bichlorid of mercury ointment, 1 : 5000, under the lids, and dressing followed the above. The following day, after staining with fluorescein, an ulcer of dendritic conformation was observed, the five vesicles having coalesced. After cauterization with a mixture of phenol, iodin, and glycerin, a dressing and pressure bandage were applied and allowed to

remain for twelve hours. The following day the fomentations, atropin, and holocain were again used at three-hour intervals. During a period of three months successive crops of vesicles occurred and from time to time coalesced. Whenever a vesicle occurred, a very faint corneal opacity resulted. Nearly the entire upper half of the cornea was involved during the three months. Pain, photophobia, and lacrimation were intermittent. The end-result was a large, irregular macula of the upper corneal segment, with vision 6/12, due to an irregular astigmatism.

CASE 2.—A white, male bank employee, aged twenty-six years, consulted me in October, 1922, complaining of supra-orbital and retrobulbar neuralgia, lacrimation, and photophobia. He had had a typical case of dengue beginning sixteen days before and lasting eight days. During the attack he had had discomfort when in the light and some lacrimation and a feeling as of sand under the eyelids. All the eye symptoms subsided with the disappearance of the fever. On the fourteenth day following the initial illness the left eye became very tender, and lacrimation, photophobia, and supra-orbital neuralgia were present.

The family history was negative. When a child, the patient had had an attack of malaria. The general physical examination was negative except for several ruptured herpetic vesicles of the left upper and lower eyelids and the ala of the nose. Wassermann, urinalysis, and examination for malarial plasmodium were negative.

There was slight photophobia and lacrimation, and the conjunctiva showed moderate injection. An arborescent ulcer, covering an area of about 2 mm., and appearing to be quite superficial, was found just below the center of the left cornea. The iris was normal, with reacting pupil. Vision was 6/5. Laboratory examinations were negative; cultures showed no growth.

Fomentations, 2 per cent. atropin sulphate, and 2 per cent. holocain, every three hours, were ordered; bichlorid of mercury ointment, 1 : 5000, was usedbetween the lids and a dressing was applied. In one week the ulcer was entirely healed, with no impairment of vision.

CASE 3.—A white merchant, aged fifty years, consulted me in October, 1922, stating that two weeks previously he had become ill. He had had a chill, followed by elevation of temperature, and what he described as "breakbone aching." The elevation of

temperature and aching had continued for five or six days, during which time he was confined to bed. Supra-orbital neuralgia had been intense, with aching and burning of both eyes. He had no rash. At the end of one week he had felt considerably improved and had returned to work. However, his eyes continued to annoy him, there being a marked degree of discomfort when he was in the bright light or at close work. The supra-orbital neuralgia had persisted. The right eye was extremely painful and felt as though there was something in it.

His family history and past history were negative. General physical examination was negative. Wassermann, urinalysis, and examination for malarial plasmodium were negative. Photophobia and lacrimation were marked. The ocular and palpebral conjunctivae were injected. There were six vesicles on the right cornea, none of which involved the exact center. Two of the vesicles were ruptured and stained deeply with fluorescein, whereas the unruptured vesicles stained only lightly. The corneal sensation was unimpaired. The iris was normal, and the pupil reacted normally. The fundus and media were normal. The tension was 25 mm. Hg (Schiötz), and vision was 6/12. The left eye was normal. Vision was 6/6 with lenses. Laboratory examinations were negative, cultures from the vesicles showing no growth. The conjunctival smear showed bacilli xerosis.

The unruptured vesicles were opened and cauterized with 50 per cent. tincture of iodin. Following this, 1 per cent. atropin sulphate was instilled. Bichlorid of mercury ointment, 1 : 5000, was used between the lids and a dressing and pressure bandage were applied. Twelve hours later the denuded areas were healing, and fomentations, 1 per cent. atropin sulphate, and 2 per cent. holocain, at three-hour intervals, were ordered, with dressing between treatments. The vesicles healed in one week, leaving very faint nebulae, the vision being 6/6 with lenses. One month later the patient was refracted, with the following result: R.E., -0.50 sph. $\bigcirc$ $+$ 1.00 cyl. ax. 135° = 6/6; L.E., $+0.25$ cyl. ax. 15° = 6/5. With addition $+2.00$ sph., the patient read J. No. 1 at 15 inches.

Case 4.—A white boy, aged four years, convalescing from an attack of dengue which had subsided one week before, came under my observation in November, 1922. The correctness of the dengue history was vouched for by the pediatrician who had attended the child. He stated that a typical rash had accompanied the illness.

The day before bringing the child to me the mother noticed that the right eye was inflamed and sensitive to light.

The family history and personal history were negative. The child was well nourished, with no physical defects other than the findings revealed after examination of the right eye. Ear, nose, and throat examination was negative.

The child had intense photophobia and lacrimation, and it was only after forcible persuasion that the globe of the affected side could be examined. The conjunctivae, ocular and palpebral, of this eye were injected. The cornea showed a narrow superficial ulceration, about 2 mm. in length, extending horizontally across the pupil. There were numerous lateral offshoots. Staining with fluorescein brought out the dendritic conformation, there being the typical arborescence due to a coalition of numerous tiny vesicles. At a few points along the course of the ulcer there was an opaqueness of Bowman's membrane and possibly of the upper layers of the substantia propria, but the lesion was characteristically one of the epithelium. The pupil was contracted, but reacted promptly to light, and there was no evidence of iritis or hypopyon. The tension taken digitally seemed to be normal. On account of the behavior of the patient ophthalmoscopic examination was unsatisfactory. The left eye was normal in all respects. Vision could not be ascertained.

The Wassermann and urinalysis were negative. Blood count: total red cells, 4,500,000; total white cells, 6,000. Differential count was not made. Malarial plasmodium was not found. Cultures taken from the ulcer showed no growth.

The cornea was anesthetized with 2 per cent. holocain, and the ulcer carefully touched with mercury bichlorid, 1 : 500. One per cent. atropin sulphate was instilled, and white vaselin was applied between the lids, followed by a dressing and pressure bandage. The following morning the ulcer was found to have progressed in both directions, it now being about 4 mm. in length. The spreading areas were cauterized, using a mixture of phenol, iodin, and glycerin, after which a dressing was applied and allowed to remain on six hours. At this time hot compresses for one hour, ½ per cent. atropin, 1 per cent. holocain, and vaselin, followed by pressure dressings, were used every four hours. On the fourth day the nasal end of the ulcer was healing, but the temporal end was continuing to progress. A number of cauterizations were done, but they seemed to be of no avail. There was considerable involve-

ment of the deeper areas of the cornea by this time. After a month a general anesthetic was given and the affected area was carefully curetted and cauterized with one-quarter strength tincture of iodin. It was found that the epithelium was very easily detached, and that there was considerable involvement below Bowman's membrane, which I took to indicate a secondary infection. A pressure bandage was applied, after using 1 per cent. atropin sulphate, and white vaselin between the lids. On the third day the bandage was removed, and it was found that epithelialization was almost complete. From this point on the recovery was uneventful. The visual result was 6/9, there being a central nebula of the cornea and a small amount of irregular astigmatism.

CASE 5.—A white male, aged forty years, was seen in consultation with one of my colleagues one week after a verified attack of dengue. The patient complained of feeling a foreign body in the left eye, lacrimation, and photophobia.

The family history was negative. The general physical examination, Wassermann, urinalysis, and examination for malarial plasmodium were negative.

There were intense lacrimation and photophobia of the left eye, with marked ciliary injection. Just below the center of the cornea was an arborescent ulcer 3 mm. in length, which was quite superficial. It stained well with fluorescein.

Fomentations, 1 per cent. atropin, bichlorid of mercury ointment, 1 : 5000, and a dressing every four hours were advised. After one week the ulcer had healed and vision was normal.

The types of keratitis most frequently reported are herpetic, dendritic, and neuroparalytic. These types, as I suggested in my paper in 1926, point to a neuropathic origin. In one of the cases I have reported here the corneal condition was attended with herpes of the eyelids and face over the area supplied by the fifth cranial nerve. The intense aching of the eyes and the supra-orbital neuralgia, together with the injection of the conjunctiva, lacrimation, and photophobia, seem to suggest strongly that in dengue there is a ganglionic toxemia, whether it be in the gasserian ganglion or even more peripheral, in the ciliary ganglion, or a neuritis of the terminal fibers. One has only to consider the

symptoms and pathologic changes of a herpes zoster ophthalmicus to picture an exaggerated symptom-complex similar to that found in dengue. In various other acute infections—namely, malaria, measles, influenza, typhoid, nasopharyngeal disease, and smallpox vaccination—the neuropathic types of keratitis, together with herpes of the skin area supplied by the fifth cranial nerve, are occasionally seen, and are no doubt due to acute ganglionitis and peripheral neuritis of the fifth cranial nerve.

Van Millingen (1889) mentioned two cases of paresis of accommodation after dengue; van Steeden (1907) published one case. Barkan (1919) reported one case of paralysis of the external rectus and one of paresis of accommodation. Gill (1926) found it impossible to state the frequency of accommodative weakness or paresis, because many of the patients, who were soldiers, failed to return for further observation after their discharge from the hospital. This failure may be explained in part by the fact that the average soldier uses his eyes very little for close work, and therefore would not seek relief for the accommodative disability. About three per cent. of all patients who had had dengue did return. The paresis of accommodation resembled the post-diphtheritic type very closely, except that it cleared up much more quickly. Gill felt that this condition was due to the direct action of a toxin upon the ciliary muscles. In 1928, in an article published in the Archives of Ophthalmology, Gill amplified his discussion of my paper. Bistis (1929) observed a case of paralysis of the external rectus muscle. Gabrielides (1929) reported two cases of paresis of the left external rectus and two cases of accommodative paresis. Bargy (1929) described one case of paresis of the third cranial nerve.

During their convalescence a number of my patients complained of difficulty in doing close work. Many of these patients had refractive errors which were known to have

been properly corrected prior to the attack of dengue. This symptom can be attributed to a reduction in the power of convergence found in 20 out of the 25 patients examined. These 25 patients had had their converging power recorded in routine refractions within two years previous to the attack of dengue. Within two weeks after the attack the power of convergence had returned to normal. The power of accommodation of a series of 50 patients was estimated, with the finding of one case of actual paresis which is reported in detail below.

CASE 6.—A white male, aged twenty years, complained of inability to do close work since an attack of dengue which had had its onset three weeks before and had lasted seven days. Preceding the attack the patient had had a severe headache of several days' duration. He stated that during the elevation of temperature, which was of the saddle-back type, he had had an intense retrobulbar aching with photophobia and lacrimation. During the acute stage of the attack the typical rash and intense bone ache were predominant features.

Eye examination, made three weeks after the onset of the disease and two weeks after its subsidence, showed the following: External examination was negative. Vision O. U. was 6/5; read J. No. 1 with + 4.00 sph. at 33 cm., O. U. The pupils were dilated to the maximum limits, with no response to light or accommodative reflex. The fundi were negative. There was external ocular muscle balance. There was a gradual return of accommodative power over a period of three months. With the return of accommodation the pupils returned to normal size. The general physical examination, including Wassermann and search for foci of infection, was negative.

The only case of ptosis complicating dengue which I have been able to find besides the one reported below was that published by Bargy. It might be expected that ptosis would be observed more frequently since complications resulting from involvement of other fibers of the third cranial nerve are not uncommon.

CASE 7.—A white male, aged forty years, consulted me fifteen days after the subsidence of a verified attack of dengue. He stated that during the acute attack he had had intense aching of the eyeballs, with lacrimation and photophobia. During the last few days of his illness he had had difficulty in raising the upper lid of the right eye. This difficulty became more marked, and on examination it was found that there was an incomplete ptosis. The right palpebral fissure measured 4 mm., whereas the left measured 10 mm. On extreme effort to elevate the right lid the fissure measured 6 mm. The eye findings were otherwise negative. The patient's vision was: R. E., with -0.50 sph. $\bigcirc$ -0.75 cyl. ax. $90° = 6/5$; L. E., with -0.75 sph. $\bigcirc$ -0.25 cyl. ax. $90° = 6/5$. The general physical examination showed nothing of interest. Routine laboratory examinations were negative. After four weeks the function of the eyelid was normal.

CONCLUSIONS

1. Considering the pandemic character of dengue and the few actual complications reported, ocular complications directly attributable to the disease are rare. Many of the complications reported are coincidental.

2. Ocular symptoms in dengue, such as retrobulbar and supra-orbital neuralgia, lacrimation, photophobia, irritation of the conjunctiva, and pain on moving the eyeballs, are the rule, but do not assist materially in diagnosing the disease.

3. Keratitis of the herpetic type is one of the more frequent complications.

4. Ocular muscle paresis is often reported as a complication, and is to be expected, since dengue is a profound toxemia.

5. The ocular symptoms and the corneal complications are undoubtedly due to the effects of the dengue toxin on the fifth cranial nerve, resulting in acute ganglionitis or peripheral neuritis.

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INTRA-OCULAR MYCOSIS*

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In medical literature the ocular mycoses have become relatively common and have inspired one author (Cavara) to produce a comprehensive volume devoted to this subject. Cases of intra-ocular mycosis are, however, extremely rare, and the accidental discovery of one case in my own practice, due to the genus aspergillus, has been the incentive for a review of the literature of this subject and the writing of this paper.

The molds, yeasts, and actinomycetes are fungi. They are a part of that subdivision of the plant kingdom known as thallophytes, the members of which, being devoid of chlorophyl, must depend for their sustenance upon organic matter synthesized by other organisms, thus growing as either saprophytes or parasites.

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